Hepatitis C Infection is Associated with Decreased Use of Lipid-Lowering Therapy 48 Weeks After Initiation of Combination Antiretroviral Therapy in the ACTG 5001 (ALLRT) Cohort

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ABSTRACT

Background: Previous studies found lower total cholesterol and low density lipoprotein (LDL) levels in HIV-positive people with hepatitis C virus (HCV) compared to those without HCV infection. To further investigate the relationship between HCV and serum lipid levels before and after initiating antiretroviral therapy (ART), we studied 1,440 antiretroviral-nave HIV-infected participants of the AIDS Clinical Trials Group 5001 (ALLRT) study. All subjects received iÂ3 agents in randomized, prospective ART clinical trials.

Methods: HCV infection was defined as HCV antibody positive (ELISA) or a clinical diagnosis of HCV. ART protocols excluded those with ALT > 5X ULN and other factors. Fasting total cholesterol, non-high density lipoprotein (HDL) cholesterol, triglyceride (TG), HDL and glucose levels were evaluated before and after 48 weeks of ART. Non-HDL cholesterol was used as LDL was not available on all subjects. Other variables examined included serum liver enzymes (ALT, AST, alkaline phosphatase), CD4, and HIV RNA before and following 48 weeks of ART. Demographics and pre-ART body mass index were also assessed. The primary analysis compared HCV-positive with HCV-negative individuals.

Results: HCV-positive subjects (11%; n=161) were older and more likely to be Black (p<0.05). As expected, those with HCV were more likely to have a history of IDU, and to have higher baseline ALT, AST, and alk phos levels (p<0.05 for all). While lipid levels went up in both groups over time, unlike prior studies, week 48 fasting cholesterol levels were not different between HCV-positive and negative subjects. Following 48 weeks of ART, changes in fasting cholesterol levels also did not differ significantly; however, 53/1242 of the HCV-negative subjects (4.1%) received lipid-lowering drugs compared to 0/161 HCV-positive subjects (p=0.003). A greater proportion of HCV-positive subjects had diabetes at baseline (5% vs. 2%, p=0.07).

Conclusions: In contrast to prior studies, cholesterol and non-HDL lipid levels were not different over time between HCV-positive and negative subjects in this cohort of antiretroviral naive patients enrolled in prospective, randomized clinical trials. This may reflect the absence of ART selection bias, and also exclusion of subjects with liver enzyme elevation >5X ULN. However, significantly fewer HCV-positive subjects required lipid-lowering agents after 48 weeks of ART, supporting a lipid-protective association with HCV infection.

Introduction

Due to shared modes of transmission, HIV-infected individuals are frequently co-infected with hepatitis C virus (HCV) [1]. Anti-HIV treatment with combination antiretroviral therapy (ART) and HCV infection are associated with insulin resistance [2] and hepatic steatosis [3]. Dyslipidemia is a major health risk for patients receiving long term ART [4,5]. The use of lipid-lowering therapy is frequently effective, but is complicated by potential drug-drug interactions, increased risk of toxicity and added pill burden. In contrast to ART, HCV infection is associated with low serum LDL and HDL levels [6,7]. Although this may reflect HCV-related cirrhosis and poor hepatic synthetic function [8], in some studies HCV infection is associated with lower total cholesterol and LDL levels compared to HCV-uninfected controls independent of the histologic stage of liver disease [7]. Low serum lipid levels are associated with HCV infection in HIV-negative and HIV-infected cohorts [2,9,10], and the effect appears to be HCV-specific, as lower lipid levels are not observed in patients with chronic hepatitis B [11]. Few data describe the relationship between HCV infection and metabolic changes in HIV-infected individuals receiving ART, although reports suggest that co-infected patients may have lower total cholesterol levels than HCV negative, HIV-infected patients, irrespective of ART [2,9,10,12,13] To specifically investigate the relationship between HCV infection, ART, lipid and glucose abnormalities, we evaluated a large cohort of HIV-infected individuals participating in the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) protocol who were ART naive upon entry into a prospective, randomized trial of combination therapy with three or more antiretroviral medications.

METHODS

Study Population: ALLRT Protocol (ACTG A5001), a longitudinal study of subjects enrolled in prospective, randomized ACTG trials or ART or ART strategies. For this study, all subjects were ART-naive when enrolled in parent trials, and relevant inclusion / exclusion criteria and ART regimens shown in Table 1. HCV status was defined by antibody testing. Non-HDL cholesterol (total chol. – HDL chol.) was used instead of LDL to avoid problems with calculated vs. directly measured LDL, and problems with high triglyceride levels. Demographics, clinical and laboratory data were analyzed before and during the first 48 weeks of ART.

Statistical Evaluation: Primary analysis examined lipid changes and HCV status between baseline (within 56 days prior ART) and change at week 48. Nondetectable HIV RNA was assigned as 50 copies/ml. Wilcoxon rank-sum and Fisher's exact tests compared baseline factors. Additional analyses included censoring subjects after lipid lowering drug initiation, and excluding subjects who did not suppress HIV RNA. The lipid values within a 16-week window around week 48 were analyzed. T-tests were used to compare HCV-positive and HCV-negative individuals followed by multivariate analysis adjusting for pre-treatment factors using linear regression. A 98% Winsorization was applied to the baseline and week 48 data (upper 1% set = 99th percentile, lower 1% set = 1st percentile) as this is less likely to affect mean and st. dev. estimates than exclusion of the extremities.

Table 1. Parent Study Characteristics: All potential treatment arms (by drug class) included in the parent protocols are listed. All subjects ≥3 drugs.

ACTG Protocol	384	388	A5014	A5095
Number of subjects	473	181	33	753
NRTI[a] only	No	No	No	Yes
NRTI + NNRTI[b]	Yes	Yes	Yes	Yes
NRTI + PI[c]	Yes	Yes	Yes	No
Exclusion Criteria				
ALT	≥ 2.5 x ULN	≥ 5 x ULN	≥ 5 x ULN	≥ 5 x ULN
AST	≥ 2.5 x ULN	≥ 5 x ULN	≥ 5 x ULN	≥ 5 x ULN
Bilirubin	None	none	≥ 1.5 x ULN	none
Platelet count	≤ 50,000/mm^3	≤ 45,000/mm^3	≥ 75,000/mm^3	≤ 40,000/mm^3
Creatinine	≥ 1.5 x ULN	≥ 2 x ULN	≥ 2 x ULN	≥ 1.5 x ULN

[a] Nucleoside Reverse Transcriptase Inhibitor
[b] Non-Nucleoside Reverse Transcriptase Inhibitor
[c] Protease Inhibitor

Table 2. Baseline Characteristics

Baseline Factor		Total	HCV Positive	HCV Negative	P-value[b]
Medication use [n(%)]					
Lipid lowering agents		14 (1%)	0 (0%)	14 (1%)	0.39
Hypoglycemic agents		26 (2%)	6 (4%)	20 (2%)	0.06
Diabetes [n(%)]		39 (3%)	8 (5%)	31 (2%)	0.07
Fasting serum levels					
Cholesterol[a] [mg/dL]		n=758 166 (139,182)	n=76 159 (137,174)	n=682 160 (140,184)	0.14
non-HDL[a] [mg/dL]		n=742 124 (103,144)	n=75 117 (92,143)	n=667 124 (104,145)	0.10
Triglyceride[a] [mg/dL]		n=672 119 (87,173)	n=73 133 (105,193)	n=599 114 (84,167)	0.055
HDL[a] [mg/dL]		n=753 35 (29,43)	n=78 33 (28,41)	n=675 36 (29,43)	0.34
Glucose[a] [mg/dL]		n=626 84 (77,90)	n=62 85 (81,92)	n=564 84 (77,89)	0.045
Body Mass Index [n(%)]					
underweight, <18.5		48 (3%)	11 (7%)	37 (3%)	0.046
normal, 18.5-25		750 (52%)	88 (50%)	662 (52%)	
overweight, 25-30		463 (32%)	43 (27%)	420 (33%)	
obese, > 30		179 (12%)	18 (11%)	161 (13%)	
Serum Levels:	ALT[a] [U/L]	n=1435 31 (21,47)	n=159 40 (26,60)	n=1276 30 (21,46)	0.004
	AST[a] [U/L]	n=1435 29 (23,40)	n=159 40 (28,56)	n=1276 29 (23,39)	<0.001
	Bilirubin[a] [mg/dL]	n=1429 0.5 (0.4,0.7)	n=159 0.5 (0.4,0.7)	n=1270 0.5 (0.4,0.7)	0.13
	Alkaline Phosphatase[a] [U/L]	n=1430 79 (65,97)	n=159 85 (69,108)	n=1271 78 (65,95)	0.003
	Lipase[a] [U/L]	n=829 33 (24,54)	n=90 37 (30,71)	n=739 32 (23,51)	0.026
	Platelet Count[a] [10^3/mm^3]	n=1422 198 (159,237)	n=156 197 (146,229)	n=1266 198 (160,238)	0.16

[a] Median (25th, 75th percentiles); [b] Fisher exact for categorical and t-test for continuous variables.

Table 3: Fasting Lipid levels and other factors before and following 48 weeks of combination antiretroviral therapy.

Parameters	HCV	N	Baseline Mean (S.E.)	Week 48 Mean (S.E.)	Change Mean (S.E.)	P[a]
Cholesterol[b]	Pos	57	157 (4)	188 (6)	31 (5)	0.78
	Neg	561	164 (1)	195 (2)	32 (2)	
non-HDL[b]	Pos	56	119 (4)	134 (6)	15 (5)	0.22
	Neg	545	127 (1)	150 (2)	22 (2)	
TG[b]	Pos	52	168 (14)	194 (24)	26 (22)	0.16
	Neg	490	142 (4)	177 (6)	35 (5)	
HDL[b]	Pos	57	39 (2)	53 (2)	14 (2)	0.011
	Neg	548	37 (0.4)	46 (1)	9 (0.5)	
Lipid drugs, n(%)	Pos	160	0	0	0	0.017
	Neg	1280	14	53	39	
CD4 cells/mm^3 median	Pos	148	253 (17)	406 (21)	152 (12)	0.019
	Neg	1243	245 (6)	426 (7)	182 (4)	
logHIV RNA copies/ml	Pos	148	4.94 (0.06)	2.14 (0.08)	-2.80 (0.10)[c]	0.018
	Neg	1244	4.98 (0.02)	1.96 (0.02)	-3.02 (0.03)[c]	

[a]difference in change of value between HCV positive and negative between pre-ART and following 48 weeks of ART; lipid comparisons based on $\log_{10}$ transformation. [b] fasting not available on all subjects. [c] $\log_{10}$ reduction in HIV RNA.

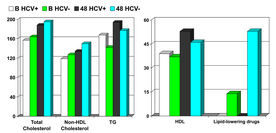

Figure 1. Fasting lipid levels and use of lipid lowering medications before and following 48 weeks of combination antiretroviral therapy. Fasting values were not available on all subjects. Note that all lipid measurements increased following combination antiretroviral therapy in both HCV-positive and HCV-negative subjects.

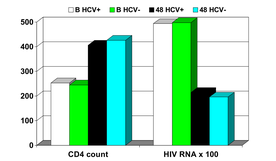

Figure 2. There were no significant differences between HCV-positive or HCV-negative subjects at either baseline in CD4 or HIV RNA.

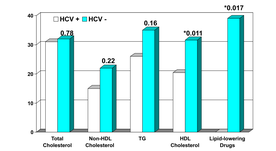

Figure 3. Change in serum lipid markers and used of lipid lowering medications following 48 weeks of combination antiretroviral therapy. The absolute change in value for total, non-HDL, triglyceride and HDL cholesterol (G/DL), and number of subjects starting lipid-lowering drugs is shown. P value for comparison (difference in change between HCV positive and negative between pre-ART and following 48 weeks of ART are shown. * = statistically significant

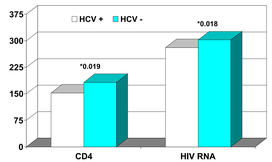

Figure 4. Change in CD4 (cells/mm3) and plasma HIV RNA concentration (value/100 x log10) following 48 weeks of combination antiretroviral therapy. P value for comparison (difference in change between HCV positive and negative between pre-ART and following 48 weeks of ART are shown. * = statistically significant

Summary

1. HCV infection present in 11% of ALLRT participants in this study (n=1,440)
2. HCV associated with IDU, older age and black race, higher ALT, AST, alkaline phosphatase.
3. Unlike prior studies, cholesterol levels were not lower in HCV-positive subjects at baseline, and TG levels were higher than HCV-negative subjects. This may reflect selection bias in prior studies, or the fact that these ALLRT studies excluded individuals with significant elevations of ALT and AST (table 1).
4. Glucose levels were higher in HCV-positive (0.045), and baseline diabetes and use of glucose-lowering medications were greater in HCV-positive, though these values did not reach statistical significance (P=0.07 and 0.06 respectively).
5. Fewer HCV-positive individuals were obese compared to HCV-negative individuals.
6. CD4 counts were not significantly different at either the baseline or following 48 weeks of ART; however, as reported in other studies, the rise in CD4 following ART was greater in HCV-negative subjects (P=0.019).
7. Similarly, HIV RNA values were not significantly different at either the baseline or following 48 weeks of ART, but fell to a greater extent in HCV-negative subjects (P=0.018).
8. All lipids (total, non-HDL, HDL cholesterol, and triglycerides) rose following 48 weeks of ART. Although the absolute values were lower in HCV-positive subjects for total, non-HDL cholesterol and triglycerides, these were not significant. HDL rose more in HCV-positive subjects (p=0.011).
9. No HCV-positive subjects received lipid-lowering drugs during this study, while 14 and 53 HCV-negative subjects received these meds baseline and 48 weeks respectively (p=0.017).

Conclusions

1. In contrast to prior studies, cholesterol and non-HDL lipid levels were not different between HCV-positive and negative subjects.
2. HDL levels rose more in HCV-positive subjects
3. Glucose levels were significantly higher in HCV-positive subjects, and a trend towards more diabetes and glucose-lowering meds was found.
4. Significantly fewer HCV-positive subjects required lipid-lowering agents after 48 weeks of ART, supporting a lipid -protective association with HCV infection.

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